52

Disorders of Hemostasis: Thrombosis

Richard Torres and Henry M. Rinder

PATHOLOGY OF THROMBOSIS

The Virchow triad defines the pathologic mechanisms underlying thrombosis: diminished blood flow, damage to the vascular wall, and an imbalance favoring procoagulant over anticoagulant factors. The first two factors are clearly localized to specific vascular beds; although the last element of the triad may be systemic, data show at least partial regulation of the hemostatic balance by anatomic region. For example, congenital deficiency of AT, protein C, or protein S typically leads to venous thromboembolism (VTE) of the lower extremities. In contrast, the inherited hypercoagulable disorders associated with the factor V Leiden and prothrombin G20210A mutations not only produce lower extremity VTE but also are associated with thrombosis of the cerebral veins and sinuses.

This hemostatic regulation in vascular tissues is mediated by multiple factors that include (1) microenvironmental signals, such as shear stress resulting from turbulence in the disrupted flow of damaged vessels, that affect endothelial cell (EC) expression of thrombomodulin, tissue factor, and nitric oxide synthase as well as platelet activation; (2) EC subtype–specific signaling (e.g., shear stress upregulates aortic, but not pulmonary artery, nitric oxide synthase); (3) differences in EC transcriptional regulation of proteins such as von Willebrand factor (vWF) and its cleaving protease, ADAMTS-13; and (4) the increasingly appreciated important link between inflammation and thrombosis that is mediated in both physiologies by selectin and integrin ligands.

Atherothrombosis

This section briefly discusses hematologic factors that predispose to thrombosis in the setting of atherosclerotic plaque (atherothrombosis); the pathophysiologic mechanisms of atherogenesis are discussed in Chapter 8.

Atherothrombosis and Fibrinolysis

In addition to EC-directed regulation of hemostasis, the interaction of EC with the fibrinolytic system is important in the development of atherothrombotic disease because it affects the degree of clot propagation. The breakdown of stable fibrin polymers into fibrin split products, including the D-dimer segments that are routinely measured in the laboratory to detect recent thrombosis, is mediated by plasmin. Plasmin is converted from its inactive form, plasminogen, by tissue-type plasminogen activator (t-PA), the activity of which is regulated by plasminogen activator inhibitor-1 (PAI-1). Abnormal levels of both t-PA and PAI-1 are epidemiologically associated with an increased risk for arterial thrombosis, but the degree to which absolute levels contribute to arterial thrombosis remains controversial. For this reason, the current clinical utility of t-PA and PAI-1 measurements is limited.

The fact that it is high t-PA levels (rather than high PAI-1 levels) that are associated with higher rates of atherothrombosis, specifically acute myocardial infarction and stroke, is a curious phenomenon. It may be a manifestation of upregulation of t-PA serving as a surrogate marker for high de novo PAI-1 levels, although a direct correlation of PAI-1 levels and overall arterial thrombosis rates remains weak. Notably, PAI-1 is markedly increased in generalized inflammation. The strong association between abnormal hemostasis and high PAI-1 levels in patients with the metabolic syndrome or vascular disease in type 2 diabetes may be related to inflammatory roles for PAI-1, emphasizing the importance of the thrombosis-inflammation interplay. Relatedly, the risk for acute myocardial infarction is elevated in the subset of patients with angina pectoris who have increased PAI-1 activity levels, and there is evidence for a direct contribution of PAI-1 levels to the risk of stent restenosis after angioplasty. From a genetic risk standpoint, the 4G isoform of PAI-1 (compared with the 5G form) results in higher levels of PAI-1 but only a small increase in relative risk for arterial thrombosis. By contrast, t-PA polymorphisms and plasminogen levels do not correlate with atherothrombotic risk.

Hyperhomocysteinemia in Arterial Disease

Increased levels of plasma homocysteine (HCY) are linked to atherothrombosis. The rare congenital syndromes (e.g., cystathionine β-synthase deficiency) that are characterized by homocysteinuria and hyperhomocysteinemia are associated with both VTE and premature atherosclerosis. Elevated HCY induces EC dysfunction and apoptosis, triggering normal coagulation pathways designed to respond to EC damage but without the corresponding upregulation of EC-dependent anticoagulant function (e.g., activated protein C [APC]). Even moderate elevations in HCY may thus contribute to coronary, peripheral, and cerebral arterial disease. Mildly elevated HCY levels are associated with the thermolabile form of the methylene tetrahydrofolate reductase (MTHFR) enzyme, which results from a polymorphism (C677T) in the coding region of the MTHFR binding site. This isoform occurs in 30% to 40% of the general population and introduces a higher set point for regulation of HCY concentration (the substrate for MTHFR), particularly when a relative folate deficiency exists. In fact, deficiency of any of the vitamin cofactors of HCY metabolism (folate, vitamin B_6, and vitamin B_{12}) may lead to mild hyperhomocysteinemia.